ADULT PATIENTS WITH UNDIAGNOSED CONDITIONS AND THEIR RESPONSES TO CLINICALLY UNCERTAIN RESULTS FROM EXOME SEQUENCING

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ABSTRACT

Patients pursuing exome sequencing in their quest for diagnosis will most often receive a clinically uncertain result. A clinically uncertain result has some level of objective uncertainty as viewed by clinicians regarding a patient's diagnosis. A clinically uncertain result can be a result that is negative, with no reportable genetic variants, or that includes one or more genetic variants deemed uncertain with regard to the cause of a patient's condition. Clinically uncertain results present challenges to both providers and patients in disclosing and processing ambiguous health information. This exploratory study sought insight into the psychological and behavioral impact of receiving clinically uncertain results from exome sequencing. Semi-structured phone interviews were conducted with 23 adult patients with undiagnosed conditions who have received two of the more common types of clinically uncertain results from exome sequencing: either a negative result or a result with one or more variants of uncertain significance. Interviews focused on the experience of receiving the clinically uncertain result, with emphasis on conceptualization of uncertainty and coping. Interviews were transcribed and subjected to thematic analysis, and results were analyzed within the context of participants' diagnostic odysseys. No thematic differences were found between the experiences of those who received negative results versus those who received one or more variants of uncertain significance. Participants demonstrated a variety of conceptualizations of the uncertainty related to their exome sequencing result and undiagnosed condition. They were generally acclimated to illness uncertainty due to their lengthy and ongoing diagnostic journey, which resulted in realistic expectations about and acceptance of their clinically uncertain results. However, participants still hoped that exome sequencing would end their diagnostic odyssey, and many remain hopeful that future technological advances will provide them with a diagnosis. This residual hope, as well as optimism, were used as coping strategies to deal with continued uncertainty. Understanding how patients with undiagnosed conditions respond to clinically uncertain results from exome sequencing can inform providers'

practices around informed consent and the disclosure of clinically uncertain results through a greater consideration of patients' reactions, concerns, and challenges with adaptation to uncertainty.

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INTRODUCTION

Exome Sequencing and Clinically Uncertain Results

The field of medical genetics is advancing rapidly, with greater use of genomic approaches such as exome sequencing. Exome sequencing is a genetic test that analyzes the exome, or the protein-coding regions of the genome, to detect known disease-causing genetic variants that may provide diagnoses for patients. The use of clinical exome sequencing is on the rise due to its clinical utility, efficiency, and cost-effectiveness (Yang et al, 2013; Bamshad et al, 2011). However, this genetic service has been incorporated into clinical practice at a much faster rate than that of the medical community's ability to collect data about the disease-causing potential of exonic variants. Therefore, the increased uptake of clinical exome sequencing has resulted in an increase in the number of clinically uncertain results. A clinically uncertain result is a result that has some level of objective uncertainty viewed by clinicians regarding a patient's diagnosis. A clinically uncertain result can be a result that is negative, with no reportable genetic variants, or that includes one or more genetic variants deemed uncertain with regard to the cause of a patient's condition.

Perhaps the most commonly recognized type of clinically uncertain result is a variant of uncertain significance (VUS), or a genetic variant that has not been clearly associated with disease and for which pathogenicity is uncertain due to a lack of evidence. Laboratories offering clinical exome sequencing may choose to include different VUSs in their test reports (Bertier et al, 2016). Laboratories typically limit the VUSs they report to those found in genes that are known to cause conditions that are related to the patient's phenotype. Yet the genes that each laboratory chooses to target may vary. Laboratories may also report VUSs that are unrelated to the patient's phenotype, such as those found in the American College of Medical Genetics and Genomics (ACMG) list of 59 reportable secondary findings. This ACMG list is a list of genes that contribute to conditions that are deemed clinically preventable or actionable (Kalia et al,

2017). In addition to VUSs, there are various other types of clinically uncertain results that can occur from exome sequencing. Among the various types of clinically uncertain results, negative results and VUSs appear to be most common (based on personal communication with genetic counselors at Johns Hopkins Hospital Genetics Clinics and Kennedy Krieger Institute).

Exome sequencing has been reported to only provide complete diagnoses to about 25% of patients with undiagnosed conditions (the specific percentage is largely dependent upon the patient's clinical presentation) (Berg, 2014; Sawyer et al, 2016; Yang et al, 2013). Therefore, undiagnosed patients receive clinically uncertain results from exome sequencing about 75% of the time. Because advancements in sequencing technologies have not been matched with increased knowledge for genetic variant interpretation, patients with undiagnosed conditions who are offered exome sequencing are more often left with uncertainty rather than a diagnosis.

Patients with Undiagnosed Conditions

Patients with undiagnosed conditions have illnesses that are rare or ambiguous enough to elude a specific molecular diagnosis. These patients have often endured a diagnostic odyssey characterized by chronic uncertainty. The term diagnostic odyssey has been used to describe the onerous and frustrating journey of seeking a diagnosis, one that involves non-diagnostic encounters with countless specialists (Basel & McCarrier, 2017). For patients with undiagnosed conditions, exome sequencing is usually part of a "last ditch" effort to attain a diagnosis (Sawyer et al, 2016). This patient population's experience with chronic uncertainty related to their illness makes them a particularly interesting and relevant population to study regarding responses to clinically uncertain results from exome sequencing.

At the outset of exome sequencing in clinical care, trios of undiagnosed children and their parents were typically those receiving the service because trio testing increases diagnostic yield (Sawyer et al, 2016). Studies of parents of children with undiagnosed conditions suggest that a

diagnosis, while not resolving all uncertainty, can significantly reduce uncertainty through providing a label, an explanation of cause, prognostic and treatment information, and avenues for social support (Madeo et al, 2012; Rosenthal et al, 2001; Carmichael et al, 2015).

While several studies have explored perceptions of uncertainty in relationship to genetic testing among parents of undiagnosed children (Macnamara et al, 2014; Madeo et al, 2012; Rosenthal et al, 2001; Graungaard et al, 2006; Lipinski et al, 2006), adults with undiagnosed conditions have only relatively recently been able to take advantage of exome sequencing, and their response to uncertainty from exome sequencing is still a relatively new phenomenon that requires exploration. Qualitative studies of illness narratives from adults with undiagnosed conditions have shown a common theme of chronic uncertainty, but these studies have not examined the impact of uncertain genetic test results (Spillmann et al, 2017; Nettleton, 2006; Nettleton et al, 2005). One might anticipate certain differences in the ways adult patients with undiagnosed conditions experience and perceive genomic uncertainty compared to parents of children with undiagnosed conditions because the adult patients are living with illness themselves.

Theoretical Framework

***Uncertainty in Illness Theory*.** In Western society, certainty, predictability, and control are the expected and desired outcomes of medicine. Physicians are expected to use scientific methods to provide accurate diagnoses and information on effective treatment. When uncertainty is the outcome, the medical endeavor is seen as deficient, disrupting an individual's sense of control. As Mishel (1990) explains, uncertainty is "the inability to determine the meaning of illness-related events and occurs in situations where the decision maker is unable to assign definite values to objects and events and/or is unable to accurately predict outcomes because

sufficient cues are lacking." Uncertainty in illness is associated with psychological distress, reduced perceived self-efficacy, and an enhanced sense of danger (Mishel, 1990; Neville, 2003).

The uncertainty in illness theory (UIT) describes how individuals process uncertainty related to their illness and how they create meaning around uncertain events. Generally, uncertainty is appraised in two ways: positively (as an opportunity) or negatively (as a danger or threat). The appraisal outcome dictates coping. If uncertainty is appraised as an opportunity, the individual may implement coping strategies to work to maintain the uncertainty. If uncertainty is appraised as a danger or threat, the individual may implement coping strategies to reduce the uncertainty. Positive psychological adaptation is most likely to occur when coping strategies manipulate the uncertainty in the desired direction based on the appraisal (Mishel, 1990).

Individuals who experience illness involving a short period of uncertainty are often able to appraise, cope appropriately based on the appraisal, and adapt to reach a new equilibrium. In contrast, individuals who experience long periods of chronic illness with continual uncertainty may appraise this uncertainty differently at different time points in their diagnostic odyssey. This evolution of appraisals poses challenges to reaching a new equilibrium. Integrating chronic uncertainty into one's sense of self is an arduous journey. Yet if uncertainty is never resolved, UIT poses that it may ultimately be evaluated as opportunistic rather than aversive. However, this re-evaluation will change the individual's world view to now rest on probabilistic and conditional thinking, as certainty and predictability are now viewed as unrealistic. An individual maintains this new world view by interacting with support resources and healthcare providers who share the same world view (Mishel, 1990).

Conceptualizations of Genomic Uncertainty. Genomic uncertainty is uncertainty derived from genomic information. Genomic uncertainty can be conceptualized through Han's *sources* of uncertainty and Babrow's *forms* of uncertainty. Han's sources of uncertainty characterize the aspects of genomic information that lead to uncertainty: *probability* represents the indeterminacy

of future outcomes that comes with genomic information; *ambiguity* represents imprecise, conflicting, or missing information regarding genomic interpretation; and *complexity* represents genomic information that is challenging to understand. Babrow's forms of uncertainty describe how individuals experience uncertainty from genomic information. First, *inherent uncertainty* arises from the genetic test or condition itself, such as the accuracy and reliability of the specific test or the complex genetic cause(s) of an illness. *Information uncertainty* arises from the information that comes from the genetic test. *Views on uncertainty* describes an individual's perception of the probability of any specific outcome from genetic testing. *Structuring of information* describes how an individual organizes or integrates genomic information into their existing beliefs and values. Finally, *personal views about knowledge* describes how individuals interpret genomic information differently based on their preexisting attitudes about the value of knowledge (Newson et al, 2016; Han et al, 2011; Babrow, 1998). Han's and Babrow's characterizations of uncertainty are indeed complementary; Han describes various sources of uncertainty from genomic information and Babrow describes different ways in which uncertainty from genomic information can be experienced and interpreted. Yet these two characterizations also somewhat overlap. For instance, Babrow's *information uncertainty* can be characterized by Han's typology. In addition, Han's *probability* uncertainty contributes to the experience of Babrow's *views on uncertainty.*

Han and colleagues have taken Han's original conceptualization of genomic uncertainty and updated it in *A Taxonomy of Medical Uncertainties in Clinical Genome Sequencing* (Han et al, 2017). This updated taxonomy includes Han's original sources of genomic uncertainty and his additional issues (the matter about which the individual is uncertain), and loci (the party or parties who experience the uncertainty) of uncertainty. The taxonomy continues to break down each source, issue, and locus into further discrete units to characterize all facets of uncertainty in genomic medicine. This extensive taxonomy can be found in Appendix A.

A clinically uncertain result can be characterized by many facets of genomic uncertainty, especially in the context of exome sequencing with the goal of providing a diagnosis for a patient with an undiagnosed condition. In this context, a clinically uncertain result is marked by the dimensions of genomic uncertainty of probability, ambiguity, and complexity. Probability uncertainty is derived from the lack of prognostic information that a clinically uncertain result provides for the patient. Ambiguity uncertainty can derive from the perceived missing information from a negative result, or may derive from the lack of evidence existing to classify a VUS. Complexity uncertainty derives from the nature of the result being challenging for some patients to understand. In addition to experiencing genomic uncertainty related to these three sources, undiagnosed patients responding to clinically uncertain results from exome sequencing may describe their experiences in relation to Babrow's categories.

Theory of Cognitive Adaptation. Taylor's theory of cognitive adaptation outlines how individuals may successfully adapt to a threatening event. Her theory states that the adaptation process occurs in three steps: "a search for meaning in the experience, an attempt to regain mastery over the event in particular and over one's life more generally, and an effort to restore self-esteem through self-enhancing evaluations" (Taylor, 1983). Meaning-making is achieved through an understanding of what caused the threatening event and how it has changed one's life. Regaining mastery centers on beliefs about personal control and requires an understanding of how one can manage the threatening event and prevent it from reoccurring. Restoring self-esteem is achieved by self-enhancing evaluations, or social comparisons in which the object of comparison allows for positive self-perceptions. Taylor posits that the adaptation process occurs through the ability to form and maintain illusions, or ways in which to perceive the facts in a more positive light (Taylor, 1983).

The theory of cognitive adaptation may apply to patients with undiagnosed conditions who receive clinically uncertain results from exome sequencing. The clinically uncertain result,

or the fact that exome sequencing did not provide a diagnosis, may be a threatening event for the patient. The theory of cognitive adaptation theorizes a process in which undiagnosed patients may cope and adapt to the threat of uncertainty from clinically uncertain results.

Perceptions of and Responses to Genomic and Illness Uncertainties

Genomic Uncertainty derived from Exome Sequencing. There are few studies that examine interpretations of uncertainty around exome sequencing, with most studies focusing on healthy individuals participating in research. A quantitative study analyzing healthy individuals who participated in a genome sequencing study reported that participants perceived genomic uncertainty as a quality of the information, citing probability and ambiguity as common factors of scientific knowledge. The participants who expected uncertainty from the genomic information they would receive typically appraised the uncertainty as an opportunity, while those who did not expect uncertainty appraised it as a threat (Biesecker et al, 2014).

A qualitative study of healthy adults and adult cardiology patients enrolled in a genome sequencing study were asked questions about their perceptions of VUSs before they underwent genome sequencing. Expectations about VUSs were mixed. Some expected VUSs from genome sequencing because of previous experiences with medical uncertainty or an understanding of the limitations of medical science, while others were surprised that an uncertain finding could exist from genome sequencing. Regarding medical action, some reported they would prioritize healthy behaviors if they received a VUS while others reported they would not focus on the VUS because their doctors would be uncertain about its health implications. Most participants were optimistic that the uncertainty associated with a VUS would be reduced by future scientific discoveries (Jamal et al, 2017). These studies underscore the importance of prior expectations, as they may influence one's appraisals of uncertainty and the ways in which one copes with or responds to the uncertainty.

Responses to Genomic Uncertainty: Variants of Uncertain Significance and Uninformative Negative Results. Studies describing adult patient perceptions and responses to genomic uncertainty have mainly focused on VUSs and uninformative negative results from single gene or gene panel tests in the context of hereditary cancer diagnoses. For example, it has been reported that about a third of patients who receive VUSs from *BRCA1/2* testing recall their test results inaccurately (Richter et al, 2014; Vos et al, 2008). Richter and colleagues reported that patients who received VUSs from *BRCA1/2* testing responded to their results more similarly to those who received negative test results than those who received positive test results in terms of risk perception, cancer worry, and uptake of surveillance and risk-reducing surgeries (Richter et al, 2014). Vos and colleagues reported that patients who received VUSs from *BRCA1/2* testing felt little general life impact, yet about a third reported changes in surveillance behavior and medical decisions. Surprisingly, they also found that most patients simultaneously recalled their VUS as non-informative but interpreted it as pathogenic, showing that an incongruent perception may act as a coping mechanism to reduce uncertainty (Vos et al, 2008). A similar incongruence was found in a study of adult cancer patients who received VUSs from cancer gene panel testing. Most participants reported high perceptions of certainty about their VUS yet had accurate recall and interpretations of their result as being a VUS (Bonner et al, 2017). Solomon and colleagues, in their qualitative study interviewing patients with inherited risk for colorectal cancer, found that most patients receiving VUSs from colon cancer panels had accurate recall, but varied in their conceptualization of uncertainty and emotional response. Both positive and negative appraisals were given to their VUS, resulting in a variety of coping strategies (Solomon et al, 2017).

A qualitative study of women who received uninformative negative *BRCA1/2* results found that the genetic test results were interpreted in multiple ways depending on the individual's beliefs about the adequacy of testing and family history of cancer. While all women described feeling shocked and expressed difficulty interpreting their results, some felt confident that they

carried an undetected variant while others believed their cancer had no genetic basis (Maheu & Thorne, 2008). A quantitative study of women who received uninformative negative *BRCA1/2* results found that women who reported high ratings of pretest perceptions of carrying a cancer-related variant were at an increased risk for sustained distress (O'Neill et al, 2009). A different quantitative study found that some women who received uninformative negative *BRCA1/2* results experienced worry or distress up to seven months after testing, and that distress and worry were directly related to personal cancer history (van Djik et al, 2006). It is important to note that these studies about uncertain negatives were all based on genetic testing of only the *BRCA1/2* genes; responses to uncertain negatives in cancer genetic testing might differ in the context of broader panel tests.

One qualitative study of patient responses to negative results from exome sequencing sampled adult patients and parents of child patients, as well as the genetics providers who returned their results, to explore the interactions that occurred during result disclosure and how patients and parents construct meaning around their results. One month post disclosure, patients and parents held the same interpretation about their results as constructed in the disclosure session, which was context-dependent and varied based on the provider's interpretation of the result and personal values. After one month, most patients and parents felt either reassured that there was no genetic cause to be found or felt promise around the potential for future technology to discover a genetic cause (Skinner et al, 2016).

In addition, another study has analyzed patient responses to clinically uncertain variants from exome sequencing (these variants included VUSs, two pathogenic variants with uncertain phase (*cis* or *trans*), and variants with uncertain or incomplete phenotypic fit for the patient's condition). It should be noted that for the non-VUS results included in this study, providers described these results as "uncertain but likely" or "uncertain but possible," illustrating that these uncertain findings have higher levels of perceived certainty by clinicians compared to that of

VUSs. This qualitative study also sampled adult patients and parents of child patients, as well as the genetics providers who returned their results, to explore the interactions that occurred during result disclosure and how patients and parents respond to their results. Most patients and parents understood their result was uncertain, yet they had various levels of detailed recollection about the degree of uncertainty or the type of result. Overall, patients and parents reported feeling prepared for an uncertain result and most regarded their result as having potential value in the future (Skinner et al, 2018).

Previous studies analyzing patient responses to clinically uncertain results present inconsistent conclusions, with some studies reporting mostly accurate recall and some reporting significant inaccurate recall (Richter et al, 2014; Vos et al, 2008; Vos et al, 2008; Bonner et al, 2017; Solomon et al, 2017). In addition, risk perception can be congruent or incongruent with accurate recall. These studies most frequently focus on VUSs and uninformative negative results from cancer gene testing, and their conclusions may not be generalizable to patient populations who seek exome sequencing, such as patients with undiagnosed conditions. Conceptualizations of illness uncertainty suggest that responses to clinically uncertain results from exome sequencing may be different from what we know about how patients respond to clinically uncertain results from more targeted tests.

Illness Uncertainty and Ambiguity Aversion. Illness uncertainty, or a state in which one lacks the ability to "explain the cause of an illness, define an illness, or make predictions about future health," has been shown to influence perceptions of exome sequencing. In a study of adult patients with undiagnosed conditions, illness uncertainty was shown to influence an individual's perception of the benefits of exome sequencing and the types of information they would hope to learn from exome sequencing. Specifically, illness uncertainty was shown to be a major motivator in the decision to pursue exome sequencing. Those who felt more illness uncertainty hoped to learn more about the cause of their own illness and personal prognostic information from exome

sequencing. Those who felt less illness uncertainty perceived the major benefits of exome sequencing as gaining information about familial recurrence risks and prognostic information for family members (Khan et al, 2015).

Ambiguity aversion is a personality trait that influences how one might approach uncertain information. Those with ambiguity aversion experience negative appraisals of uncertainty and avoid making decisions when they encounter ambiguity. Ambiguity aversion has been reported to be associated with lower intentions to learn more about or share exome sequencing results among healthy research participants (Taber et al, 2015).

OBJECTIVES AND SPECIFIC AIMS

The demand for clinical exome sequencing is outpacing the developments necessary for more comprehensive genetic variant interpretation, thus resulting in growing diagnostic uncertainty from exome sequencing results. This genomic uncertainty may only be reduced when the medical community has more data about the disease-causing potential of exonic variants (Newson et al, 2016). There is only a small body of literature focusing on how patients respond to uncertain genomic information. These studies prioritize parents of children with undiagnosed conditions and patients who seek cancer gene testing and are not necessarily generalizable to patient populations seeking exome sequencing. The purpose of this exploratory study was to understand the experiences of adult patients with undiagnosed conditions who have received two of the more common types of clinically uncertain results from exome sequencing: either a negative result, or a result with one or more VUSs.

Aim 1: To understand how adult patients with undiagnosed conditions recall and perceive their clinically uncertain result from exome sequencing. This aim explored the extent of the patients' recall of their clinically uncertain result, including their understanding of the limitations of a clinically uncertain result due to its uncertain nature. It also explored how patients conceptualize the uncertainty related to their clinically uncertain result, as well as their perceptions of the relationship between their clinically uncertain result and the cause of their condition.

Aim 2: To describe common affective and behavioral responses adult patients with undiagnosed conditions report when receiving a clinically uncertain result from exome sequencing. This aim explored how patients describe and categorize their emotional reactions to receiving clinically uncertain result from exome sequencing. It also explored how patients describe their behavior in response to clinically uncertain result disclosures, such as use of coping strategies.

Aim 3: **To compare the experiences of patients who received a clinically uncertain negative result versus one or more VUSs from exome sequencing.**

METHODS

Participants

Participants were adult patients with undiagnosed conditions who have received one of the more common types of clinically uncertain results from exome sequencing: either a negative result or one or more VUSs. Participants were recruited from Johns Hopkins Hospital Genetics Clinics (JHHGC) and Kennedy Krieger Institute (KKI). The following were the eligibility criteria.

Inclusion criteria:

- Had endured a diagnostic odyssey of at least six months before receiving exome sequencing. A diagnostic odyssey may be defined as (1) having a set of clinical symptoms but no diagnosis, (2) having a clinical diagnosis of a broad category of disease (i.e. ataxia, muscular dystrophy) but no specific diagnosis, or (3) having a clinical diagnosis composed of psychosomatic and/or descriptive diagnoses that individually define single symptoms or groups of symptoms (i.e. migraines, IBS, joint pain), but that do not explain the entire phenotype.
- *And* Had exome sequencing in an attempt to attain a specific molecular diagnosis.
- *And* Received post-test counseling for exome sequencing by a genetic counselor.
- *And* Received a clinically uncertain result (a negative result with no reported genetic variants OR one or more VUSs) from exome sequencing.
- *And* Result disclosure for exome sequencing occurred anywhere from one week to seven years prior to being interviewed.

Exclusion criteria:

- Exome sequencing results provided a molecular diagnosis for the patient that does not fall into one of the above inclusion categories.
- Patient was under age 18 years at the time of clinically uncertain result disclosure.
- Patient has a cognitive disability that prevents him/her from comprehensibly answering interview questions.
- Patient cannot speak or understand English.

Procedures

Patients from JHHGC and KKI who met eligibility criteria were identified from institutional databases by the genetic counselors at each recruitment site. The genetic counselors first contacted these patients to ask for permission for their name and contact information to be shared for recruitment outreach by the lead investigator, AN (see recruitment script for genetic counselors in Appendix B). Eligible patients were contacted by AN by phone, email, or mail for recruitment. They were sent or told information about the purpose and procedures of the study (see recruitment materials in Appendices C, D, and E). Interested patients were then sent a consent form and two short questionnaires, and phone interviews were scheduled (see consent form and questionnaires in Appendices F, G, H, and I). The questionnaires were the *Intolerance of Uncertainty Short Form Scale* (Carleton et al, 2007) and the *Perceptions of Uncertainties in Genome Sequencing (PUGS) Scale* (Biesecker et al, 2017). Participants were instructed to answer the questionnaires in preparation for the interview. During the phone interview, AN asked the participant to read aloud their responses to the questionnaires and she recorded the responses on a form. The questionnaire responses were used to characterize the study sample.

Intolerance of Uncertainty Short-Form Scale: Intolerance of uncertainty is "the tendency of an individual to consider the possibility of a negative event occurring unacceptable,

irrespective of the probability of occurrence." Individuals with a higher intolerance of uncertainty tend to worry more and feel more anxious (Carleton et al, 2007). *The Intolerance of Uncertainty Short Form Scale* is a 12-item scale. The items on the scale are questions that address how one might feel in a common uncertain situation. The questions are framed with a Likert scale ranging from 1-5, with 1 being "Not at all characteristic of me" and 5 being "Entirely characteristic of me." Higher scores convey greater intolerance of uncertainty.

PUGS Scale: The *PUGS* scale measures "patients' perceptions of uncertainties regarding the clinical, affective, and evaluative implications of genome sequencing results." Specifically, this scale has items that evaluate individuals' perceptions of ambiguity, ambivalence towards learning results, medical ambiguity aversion, and uncertainty after result disclosure (Biesecker et al, 2017). The *PUGS* scale is a 10-item scale. The items on the scale are questions that address feelings of certainty about different aspects of a genetic test result. The questions are framed with a Likert scale ranging from 1-5, with 1 being "Very Uncertain" and 5 being "Very Certain." Higher scores convey greater certainty in patients' perceptions of their genome sequencing results.

When signed consent forms were returned to AN, the genetic counselors at each recruitment site provided her with the following clinical information about their patients: clinically uncertain result type (either VUS or uncertain negative - but not information about the specific genetic change(s)), number of days between the date the patient elected exome sequencing and the date the patient received their results, and the month and year the patient received their exome sequencing results. Participants consented to this information being shared with the study team by signing the consent form.

Phone interviews were only conducted if participants returned their signed consent form. Phone interviews were conducted solely by AN between August and October of 2018. Interviews typically lasted 45-60 minutes and began with the collection of demographic information and questionnaire responses. The interview then transitioned to the use of the semi-structured

interview guide, which focused on the experience of receiving a clinically uncertain result from exome sequencing, with emphasis on conceptualization of uncertainty, coping, and other affective and behavioral responses. The interview guide was developed based on the specific aims of the study as well as interview guides from existing similar qualitative studies. It was driven by open-ended questions, but included specific prompts to elicit more specific information from the participants (see interview guide in Appendix J). After the first few interviews were completed, the interview guide was adjusted slightly by reframing certain questions and changing the order of a few questions to enhance clarity, improve the flow of the interview experience, and better elicit information from participants.

Data Analysis

Interviews were audio-recorded and transcribed by an outside transcription company. Transcripts of interviews were explored solely by AN using thematic analysis, which allows for the identification of common themes and patterns within the interview transcripts. First, coding was conducted using NVivo, a qualitative data analysis software. A preliminary codebook of *a priori* codes was created based on topics from the interview guide, such as "hopes and expectations," "coping," and "recall and understanding." This preliminary codebook was applied to several initial transcripts from both participants who received negative results and those who received VUSs to confirm the codebook applied to both groups of transcripts. While applying the *a priori* codes to the first set of transcripts, some emerging codes were identified and added to the codebook, such as "motivations," and "feeling differently about cause of condition." Once the initial codebook of *a priori* and emerging codes was established from coding the initial transcripts, sub-codes were created for various codes and the initial coded transcripts were re-coded to include the sub-codes. The final codebook was then used to code the remaining transcripts. AN met periodically with her committee members during the coding process to discuss the development and organization of codes and monitor progress. Code saturation, or the

point in which no additional concepts or codes can be found in the data, was confirmed by the final codebook remaining stable during the process of coding the remaining transcripts (Hennink et al, 2017).

Once coding was completed, findings were interpreted via thematic analysis. First, coded data was separated into various groups for multiple types of comparative analysis, in which grouped data was analyzed side by side to detect any possible differences in emerging themes. The comparative groups were as follows: VUSs vs. negative exome sequencing results, "high" vs. "low" responses to the questionnaire data, and shorter vs. longer time since result disclosure. "High" and "low" groups for responses to questionnaire data were created based on the median score possible for each questionnaire (*PUGS* possible median score is 30, "low" = responses 10-29, "high" = responses 30-50; *Intolerance of Uncertainty* possible median score is 36, "low" = responses 12-35, "high" = responses 36-60). Shorter time since result disclosure was defined as one week to 12 months, and longer time since result disclosure was defined as greater than 12 months. As a whole, the coded data was then reviewed and grouped into potential themes. Potential themes were refined by providing clear names and definitions and assessing how each theme was related to the overall data set and the specific aims of the study. Themes were analyzed within the context of participants' diagnostic odysseys. Coded data within each theme was reviewed to select illustrative quotes.

RESULTS

A total of 32 participants were contacted during recruitment. Twenty-seven individuals were reached during recruitment and expressed interest in participating in the study. They were sent consent forms and had interviews scheduled. Four of these 27 individuals either did not return their consent form or were unable to be reached for the phone interview. Therefore, the response rate was 72% (23/32). Of the 23 total participants, 12 were recruited from JHHGC and 11 were recruited from KKI. Twenty-three interviews and questionnaires were collected; 14 were from participants with VUSs and 9 were from participants with negative results. One interview from a participant with a VUS was dropped from data analysis because the interview revealed that his exome sequencing results provided him with a diagnosis.

Participants had exome sequencing between 2014 and 2018. The study sample was mostly Caucasian (n=22), over half were male (n=14), and the sample was fairly well-educated. Participants widely varied in their intolerance of uncertainty and perceptions of genomic uncertainty and had a range of symptomatology (Table 1).

Table 1 Demographics and characteristics of the study participants.

Characteristic	**Participants with VUSs Result (N=14)**	**Participants with Negative Result (N=9)**
Age at Time of Recruitment, Range	28-69	29-71
Male, %	79% (11/14)	33% (3/9)
White, %	91% (13/14)	100% (9/9)
Estimated Annual Household Income	<$45,000 2 $45,000-$89,999 1 ≥$90,000 10 Declined to answer 1	<$45,000 3 $45,000-$89,999 1 ≥$90,000 5
Education	Graduate School 8 College Graduate 5 Some College 1 High School 0	Graduate School 1 College Graduate 6 Some College 1 High School 1
Length of Diagnostic Odyssey	6 months – 1 year 1 3-4 years 5 5-10 years 2 over 10 years 6	6 months – 1 year 0 3-4 years 2 5-10 years 5 over 10 years 2
Approximate Time Passed Since Exome Result Disclosure, Range	1 month – 4.25 years	6 months – 2.5 years
Category of Undiagnosed Condition[3]	Neurologic/Ataxia 7 Myopathy 3 Cardiovascular 1 Connective Tissue 1 Ambiguous 2	Neurologic/Ataxia 3 Myopathy 2 Cardiovascular 1 Connective Tissue 0 Ambiguous 3
Intolerance of Uncertainty Short-Form Scale[1], mean (SD)	25.9 (8.34)	30.4 (8.50)
Perceptions of Uncertainties in Genome Sequencing Scale[2], mean (SD)	36 (9.90)	32.2 (6.38)

1. Intolerance of Uncertainty Short Form Scale: Higher scores convey greater intolerance of uncertainty. Range: 16-48
2. Perceptions of Uncertainties in Genome Sequencing Scale: Higher scores convey greater certainty in patients' perceptions of their genome sequencing results. Range: 20-50
3. Based solely on participant report of their symptoms. Ambiguous refers to a symptomatology that does not fit into one distinct category.

All participants had unique stories about how they ended up having exome sequencing. Some self-referred themselves to the genetics clinic after doing online research or searching for recommendations on advocacy or support group websites. Others were simply referred by a provider to the genetics clinic after exhausting all other diagnostic avenues.

No thematic differences were detected during comparative analysis, which further confirmed data saturation within the total data set. Interviews uncovered four major themes: conceptualizations of uncertainty, acclimation to illness uncertainty, hope, and optimism.

Conceptualizations of Uncertainty

Participants generally had an accurate understanding of their clinically uncertain results. Those with negative results could articulate that there were no reportable findings through conveying that 'the test found nothing' or that they had not learned anything new about their condition from their results. For example, one participant described the takeaway message she understood of her negative result:

> *"But I guess what I came away with was it was another sort of dead-end because I didn't get any results."* (P5, Negative, Ambiguous)

Twelve of the 13 participants with VUSs could describe that exome sequencing detected something that their genetics providers could not say with certainty explained their condition at the current time. Yet when demonstrating this conceptual understanding of a VUS, only one participant recalled the term "variant of uncertain significance" when asked about the 'type' or 'classification' of their exome sequencing result (she reported that she only remembered the term because she recognized it on the consent form for our study). Instead, a variety of other terms were used to describe the VUSs. For instance, one participant described his VUSs as uncertain "abnormalities:"

> *"There's nothing definitive here but we do see some abnormalities that if we were to potentially take a deeper dive, or in future advancements in the studies, they might be able to tell."* (P17, VUSs, Neurologic/Ataxia)

Another participant also described his VUSs as uncertain but used different phrasing to describe the findings:

> *"They found some things that were slightly unusual but they did not know what those were an indication for."* (P24, VUSs, Neurologic/ Ataxia)

The fact that the term "variant of uncertain significance" was not memorable may suggest that the phrase itself is not necessary for adult undiagnosed patients to comprehend the nature and implications of this type of result. Almost all participants did not use genomics jargon but instead chose layman terms to describe their VUSs. While these words do not precisely define what a VUS is, the participants still demonstrated a conceptual understanding that their result was an uncertain finding that their genetics providers could not use to provide a diagnosis. Regardless of the type of result, all participants had at least a gist understanding that their exome sequencing result was clinically uncertain, therefore not providing a molecular diagnosis, a prognosis, or any guidance related to treatment or management of symptoms.

The participants conceptualized the uncertainty related to their exome sequencing result in multiple ways. These conceptualizations can be described using Han and colleagues' taxonomy of genomic uncertainties (Han et al, 2017). Participants identified *probability uncertainty* through their understanding that their exome sequencing result did not provide prognostic information. One participant expressed this probability uncertainty when describing how her hope for a prognosis by exome sequencing was not met:

> *"I was hopeful that I would have an explanation and that we would be like, 'Well, this is it, and this is what's going to happen, and this is how your life is going to be.' But that didn't happen."* (P1, VUSs, Neurologic/Ataxia)

Ambiguity uncertainty was marked by the participants' understanding that current genomics knowledge is not advanced enough to provide a diagnosis from exome sequencing. One participant, while describing what he learned during his result disclosure, demonstrated this ambiguity uncertainty:

> *"Although they don't know what they don't know, either. There's always a possibility there could be something there, but they just don't know."* (P19, Negative, Neurologic/Ataxia)

Some participants perceived a nonexistent recurrence risk for their undiagnosed condition based on their clinically uncertain result. They did not demonstrate an understanding that despite not having a molecular diagnosis by exome sequencing that there is still the possibility for hereditary transmission of their condition. For instance, when asked about what implications his clinically uncertain result had for family members, one participant said about recurrence risk:

> *"Well, I was concerned about family members, and how it might affect any nieces or nephews, brothers or sisters, and I was assured that that would not be the case based on what they learned from the exome sequencing. So that was good. That was a relief."* (P9, VUSs, Myopathy)

This misunderstanding of a more nuanced genetics concept may reflect *complexity uncertainty,* as this aspect of their result is challenging to understand. However, it may also reflect a desire for the clinically uncertain result to have some useful meaning or a realization that their result rules out some number of known heritable conditions.

Uncertainty was also conceptualized as a 'lack of identity,' which may fall under *person-centered issues of uncertainty* in Han and colleague's taxonomy. For many participants, being undiagnosed meant that a significant part of their identity was undefined, which could feel isolating. Receiving a diagnosis would mean achieving that missing identity and being able to join an identifiable group of members with the same known condition. Being a part of such a group has certain benefits, like access to support groups and the ability to qualify for participation in research studies. When asked directly about participation in support groups and research studies, many participants expressed that they desired these opportunities, but their undiagnosed

status made them difficult to find. For example, one participant described the challenge of finding the right support group:

> *"As far as support groups or whatever it's kind of difficult because I don't fit in with anyone. I'm unique."* (P5, Negative, Ambiguous)

Babrow's forms of uncertainty can also be used to describe how our participants experienced the uncertainty from their exome sequencing result (Babrow, 1998). For instance, *structuring of information* denotes how an individual integrates genomic information into their existing beliefs. Regarding the effects of clinically uncertain results on beliefs about the cause of their undiagnosed condition, most participants reported that their exome sequencing result reinforced their previous belief that their condition had either a genetic or non-genetic cause. For instance, one participant's VUS reinforced her belief that her undiagnosed condition had a genetic cause. She described her VUS as being in only one allele of a gene known to cause an autosomal recessive condition that is similar to her constellation of symptoms. She expressed that she believes she has a milder version of this recessive condition that is caused by her single genetic variant. She believes that in the future, geneticists will learn that a milder form of her condition can be caused by a single allelic pathogenic variant. She explained:

> *"I guess it makes me more confident that there is a genetic explanation, as strange as that sounds. I do think that it's not a coincidence that I have this one defective gene that's related to* [name of condition]. *Even though they don't think that the characteristics are expressed if you only have one gene, I think that maybe there's something that they just don't know, maybe [I] don't have the full* [name of condition]. *So to me it confirms that there's something there; they just haven't quite figured it out yet."* (P18, VUSs, Connective Tissue)

On the other hand, participants also spoke about how their clinically uncertain result reinforced the belief that the cause of their undiagnosed condition was non-genetic. For example, one participant spoke about how his inconclusive result reinforced his belief that his condition was

caused by rare side effects of a medication he once took to regulate his cholesterol (P3, VUSs, Myopathy). Another participant shared how his VUS reinforced his belief that Lyme disease explained his undiagnosed condition (P12, VUSs, Cardiovascular). Finally, a participant spoke about how her clinically uncertain result reinforced her belief that her condition is non-genetic because no one else in her family has similar symptoms:

> *"I think it's most likely not genetic because nobody else that I've ever heard of in a hundred relatives has ever had it. And I know it can be a spontaneous genetic issue, that this can start with me-- I understand that-- but for some reason I just don't think it is."* (P20, Negative, Neurologic/Ataxia)

Babrow's term *inherent uncertainty* describes the uncertainty that arises from the undiagnosed condition itself. Most participants reported that their clinically uncertain result reminded them of the inherent uncertainty of their undiagnosed condition, specifically the uncertainty around cause, prognosis, and treatment or cure. The response to remembering this inherent uncertainty during result disclosure was described by most participants as disappointment or frustration. For example, one participant described how each inconclusive test result received during her diagnostic odyssey makes her feel frustrated:

> *"I'm kind of used to the frustration, but it is a little frustrating that every time I go in, they're like, 'Oh, you've got this, this, this, this,' but they don't really know."* (P14, Negative, Ambiguous)

Another participant described her disappointment about exome sequencing not resolving the inherent uncertainty of the cause of her condition:

> *"I was totally disappointed because I wanted an answer and I thought, you know, I don't even care if I'm diagnosed with something, I just want to know what this is…"* (P13, Negative, Cardiovascular)

Acclimation to Illness Uncertainty

According to Mishel's uncertainty in illness theory (UIT), individuals who experience chronic illness uncertainty ultimately believe that certainty and predictability regarding their condition are unrealistic (Mishel, 1990). Our participants' expectations about exome sequencing relieving some of their illness uncertainty aligned with the UIT. All participants expressed a belief that exome sequencing was unlikely to provide results that relieved illness uncertainty. In other words, they expected a clinically uncertain result rather than one that would provide a diagnosis, prognosis, or information about treatment for their condition. While many participants mentioned that their genetics provider was diligent about informing them of the small likelihood of a diagnostic result during pre-test counseling, participants mostly contributed their expectations about clinically uncertain results to having a history of receiving inconclusive medical test results during their previous diagnostic experiences. One participant illustrated how her diagnostic odyssey influenced her expectations:

> *"What I think of in the course of battling this for almost 20 years I've kind of learned to lower my expectations and not expect a lot."* (P5, Negative, Ambiguous)

Essentially, participants were used to receiving inconclusive medical tests results, and therefore expected their exome sequencing result to also be inconclusive.

This expectation of continued illness uncertainty was also revealed when participants were asked about their initial emotional response to receiving their clinically uncertain result. Some participants expressed that their response was neutral because they expected an inconclusive result and are used to receiving these types of results from medical tests. For example, one participant described his response to his result as:

> *"I didn't have a huge reaction to it because it said what I expected it to say… But it didn't upset me; it didn't really have any negative effects, nor a positive effect because it didn't really tell me anything. So I guess I'd say I had a fairly neutral reaction to it."* (P11, VUSs, Myopathy)

Being acclimated to illness uncertainty allowed participants to more easily accept and move on from the additional uncertainty added by this most recent clinically uncertain result. When describing their coping strategies for dealing with the uncertainty from their exome sequencing result, many participants reported the use of acceptance. Specifically, the phrase *"it is what it is"* was used quite often to express the acceptance of the uncertainty related to their exome sequencing result and subsequently their undiagnosed condition. This phrase also seemed to capture the sentiment of being acclimated to illness uncertainty. One participant described being able to easily accept his clinically uncertain result because he has received those types of results in the past:

> *"I've grown accustomed to receiving that, 'Oh we don't know what it is,' kind of diagnosis. I'm just like, let's just move on…"* (P6, VUSs, Neurologic/Ataxia)

Many expressed spending limited or no time dwelling on their exome sequencing result or "moving on" from their result disclosure experience relatively quickly because their result had little impact on their lives or understanding of their condition. One participant articulated this acceptance by saying:

> *"I have the same information that I had at the time, which is kind of a non-answer… and it's still that way. […] No, I don't really spend time thinking about it."* (P18, VUSs, Connective Tissue)

This minimal impact of their clinically uncertain result explains why most participants did not report feeling differently about their exome sequencing results over time. For example, one

participant simply explained why he feels the same about his clinically uncertain result two and a half years after receiving it:

> *"So that's why my attitude […] hasn't changed because nothing new came up to affect anything."* (P26, Negative, Myopathy)

Hope

Despite participants universally expecting that it was unrealistic for exome sequencing to relieve illness uncertainty, all participants still hoped that it would. Participants' primary motivation for electing exome sequencing was driven by their residual hope that the genetic test could provide a diagnosis. How a diagnosis could specifically relieve illness uncertainty was different for different participants. Some hoped that a diagnosis could provide clarity about the chance that other relatives would inherit their condition. When describing his motivations and hopes for electing exome sequencing, one participant said:

> *"It was just knowing that this condition that I have wouldn't be passed on to my children. That was basically-- for me, that's what I was hoping to hear from it…"* (P19, Negative, Neurologic/Ataxia)

Others hoped that a diagnosis would relieve prognostic uncertainty or provide specific guidance for treatment or management of symptoms. For example, when describing his hopes for what exome sequencing could provide, one participant said:

> *"I think information that […] could help me have a better idea of what might be going on with me and help plan for the current and the future I think would be beneficial."* (P9, VUSs, Myopathy)

Additionally, another participant explained his hope for a treatment from his exome sequencing result:

> *"Well, I was willing and anxious to do anything that might lead to a proper diagnosis and then a treatment program that might reverse the decline that I was experiencing in the muscles in my back."* (P26, Negative, Myopathy)

Finally, some hoped that a diagnosis could make them eligible to participate in clinical trials related to their condition. Participation in these studies meant contributing to efforts aimed at relieving uncertainty about their undiagnosed condition.

Participants also expressed hope regarding the promise of newer technologies or advances in genomics knowledge aiding in relieving illness uncertainty in the future. This hope was expressed in two different ways. First, it was expressed in the context of participants understanding the limitations associated with the exome sequencing test. While many described exome sequencing as being the most comprehensive genetic diagnostic test available, some demonstrated the additional understanding that the test's diagnostic utility only stretches as far as the current state of genomics knowledge. In other words, some understood that there may still be a genetic explanation for their condition that has yet to be discovered, but exome sequencing is not able to detect it at this time. For example, one participant demonstrated an understanding of this concept when discussing what he learned during pre-test counseling:

> *"Just because it's not there, there's other genes that we haven't unlocked yet that may be causal."* (P23, VUSs, Neurologic/Ataxia)

This more nuanced understanding of a limitation of exome sequencing may be explained by the fairly well-educated demographic of our sample or detailed pre-test counseling. Nevertheless, this understanding reflects hope in advances in genomics knowledge producing a diagnosis in the future. Second, hope was expressed in the context of motivations for electing exome sequencing. Specifically, some participants were motivated to have exome sequencing because they knew their genetics provider could reanalyze their exome sequencing results or genomic data in the future. For instance, one participant recalled learning about reanalysis during result disclosure:

> *"Sometimes new medical science goes on, they get new, more information about causes of ataxia or places it can be, genes it can be in, and sometimes they like to retest things, and sometimes they actually get a diagnosis on the second testing…"* (P20, Negative, Neurologic/Ataxia)

This motivation demonstrates hope that reanalysis may provide a molecular diagnosis in the future. Participants who expressed hope in these two ways illustrate how hope for a diagnosis may persist despite the disappointment and frustration that is associated with receiving a clinically uncertain result or despite acclimation to illness uncertainty. This persistent hope was often reported as a coping mechanism for dealing with the uncertainty not only of their exome sequencing result but of their undiagnosed condition. For instance, when describing long-term coping with uncertainty, one participant said:

> *"[I'm] Optimistic that technology is advancing so much that I feel somewhat confident that I'll get some answers sooner rather than later."* (P9, VUSs, Myopathy)

Another participant explained how she uses hope as a coping strategy:

> *"…there's hope in science. And the genetic field is just kind of exploding and taking off. There's so many new developments and discoveries and ways that they're using the information that they're gleaning that it's very hopeful for the future."* (P5, Negative, Ambiguous)

Optimism

Participants described optimism as another coping strategy for dealing with uncertainty related to their exome sequencing result and their undiagnosed condition. Many participants explicitly mentioned having positive attitudes, while others demonstrated optimism through social comparisons to others who are perceived to be in worse situations. For example, one

participant explained how surviving many cardiac events helped him to learn to be grateful for each day, a lesson that he feels not many people learn:

> *"I'm just trying hard to be a glass-half-full guy-- but I consider this whole episode to be an absolute gift to me because I'm a healthy, active, middle-aged guy, and I've had these near-death experiences and I walked away, and I'm still a healthy, active, middle-aged guy, and I can do everything that I want to do, and I've been reminded that […] tomorrow is not promised, and live for today, and I wake up in the morning every morning and I'm happy just because I wake up, and I think a lot of people don't get to enjoy that."* (P12, VUSs, Cardiovascular)

Another participant consistently brought the conversation back to his optimistic spirit when describing his response to his clinically uncertain result, saying:

> *"I just stay positive about life. There's enough bad stuff and, like I said, a lot of people are dealt some unfortunate things, much worse than me."* (P9, VUSs, Myopathy)

Participants also demonstrated optimism through describing their emotional responses to and perceptions of the meaning of their clinically uncertain result. For example, positive attitudes were expressed when participants, like these two, reported feeling relief or happiness that exome sequencing, while not providing a diagnosis, at least did not detect a terminal diagnosis or ruled out some terminal or severe diagnoses:

> *"I mean, I guess I would rather not have an explanation for what has happened to me than to say, 'Oh, you have brain cancer,' or 'You have this.' So I was very happy in a way…"* (P1, VUSs, Neurologic/Ataxia)

> *"…it's good to rule out all the really bad stuff and no causative mutations."* (P13, Negative, Cardiovascular)

A few participants also reported relief and happiness related to exome sequencing not detecting any ACMG secondary findings. While a clinically uncertain result from exome sequencing does

not directly relieve diagnostic uncertainty, optimism is employed by some individuals to feel that exome sequencing somehow indirectly relieves some illness uncertainty by ruling out certain diagnostic possibilities or confirming some level of healthiness. These types of positive responses to clinically uncertain exome sequencing results reveal how optimism can be used as a coping strategy to reduce some of the associated uncertainty (Mishel, 1990).

DISCUSSION

The purpose of this study was to explore and describe the experience and impact of adult patients with undiagnosed conditions receiving clinically uncertain results from exome sequencing. Participants demonstrated a variety of conceptualizations of the uncertainty related to their exome sequencing result and undiagnosed condition. They were generally acclimated to illness uncertainty due to their lengthy and ongoing diagnostic process, which resulted in realistic expectations about and acceptance of their clinically uncertain results. However, participants still hoped that exome sequencing would end their diagnostic odyssey, and many remain hopeful that future technological advances will provide them with a diagnosis. This residual hope, as well optimism, were used as coping strategies to deal with uncertainty. Optimism was particularly demonstrated through the use of self-enhancing evaluations. Taylor's theory of cognitive adaptation emphasizes that adaptation to illness uncertainty is partly accomplished by these self-enhancing evaluations, which help restore an individuals' self-esteem and perception of self-control (Taylor, 1983).

Code saturation was reached within the study sample, and analysis demonstrated that there were no thematic differences between coded data from participants who received negative exome sequencing results vs. that from those who received VUSs. This finding suggests that adult patients with undiagnosed conditions may likely have similar affective and behavioral responses to receiving a clinically uncertain result from exome sequencing regardless of the type of result. It appears that the type of inconclusive result has little influence on how adult undiagnosed patients conceptualize and cope with the genomic and illness uncertainty their result encompasses. Instead, the inconclusive nature of negative results and VUSs is equivalent, in that either way the result provides no diagnostic or prognostic clarity.

Participants' responses to the *Intolerance of Uncertainty* and *PUGS* scales revealed that our sample widely varied in their reported levels of intolerance and perceptions of uncertainty

related to their exome sequencing results. While there were no thematic differences when comparing data from participants who scored “high” vs. “low” on these scales, our sample size may be too small to detect significant differences between these groups. Nevertheless, this finding might suggest that intolerance and perceptions of uncertainty may not influence the ways adult patients with undiagnosed conditions cope with and adapt to uncertainty from clinically uncertain results from exome sequencing, perhaps because of their acclimation to illness uncertainty. This suggestion differs from what we know from other quantitative studies involving healthy individuals (Biesecker et al, 2014), and of course, larger-scale quantitative studies would need to be conducted to validate such a conclusion.

Our participants had particularly good recall and understanding of their clinically uncertain results from exome sequencing. This finding from our qualitative study differs from mostly quantitative studies of cancer patients receiving clinically uncertain results from targeted cancer gene panels, which tend to report incongruent recall and understanding (Richter et al, 2014; Vos et al, 2008; Vos et al, 2008; Bonner et al, 2017; Solomon et al, 2017). Adult patients with undiagnosed conditions may have better recall and understanding than cancer patients because they are more familiar with illness uncertainty and are used to receiving inconclusive medical test results. In contrast, individuals who qualify for cancer genetic testing tend to have a strong family history of cancer, which may strengthen perceptions of certainty or act as evidence to support expectations for receiving a diagnostic genetic test result rather than a clinically uncertain genetic test result.

Expectations for uncertain genetic test results due to acclimation to illness uncertainty have been described in some of the limited number of qualitative studies related to genomic uncertainty. For instance, some healthy adults and adult cardiology patients reported expecting VUSs from genome sequencing because they had previous experiences with medical uncertainty (Jamal et al, 2017). Additionally, adult undiagnosed patients and parents of undiagnosed child

patients reported feeling prepared for an uncertain result after receiving clinically uncertain results from exome sequencing. (Skinner et al, 2018). Persistent hope that uncertainty will be resolved by future scientific advances has also been found in some other qualitative studies on genomic uncertainty. For example, healthy adults and adult cardiology patients reported expectations that such advances will aid in reclassifying VUSs from genome sequencing (Jamal et al, 2017). In addition, adult undiagnosed patients and parents of undiagnosed child patients felt similar hopes after receiving negative exome sequencing results (Skinner et al, 2016).

The findings from this exploratory qualitative study are not intended to be representative of all adult patients with undiagnosed conditions who receive clinically uncertain results from exome sequencing. Our participants were fairly well-educated, which may influence their ability to more accurately recall and understand their exome sequencing results. Participants were recruited from two different clinical sites, adding variation to the genetic counseling they received. While this allowed for some diversification in understanding the ways adult undiagnosed patients may be influenced by their result disclosure, result disclosure of clinically uncertain results by other genetic counselors may differ from the practices of the genetic counselors from our two recruitment sites. In addition, our study sample had a wide variety of symptomatology of their undiagnosed conditions. While this variety allowed us to capture over-arching themes, perhaps more nuanced differences may be detected from studying adult undiagnosed patients with more similarly presenting undiagnosed conditions. It should also be noted that as exome sequencing is offered earlier in the diagnostic process for individuals in the future, reactions to uncertain genomic information may differ.

PRACTICE IMPLICATIONS & RESEARCH RECOMMENDATIONS

The experiences reported from participants in this study have implications for the clinical practice of genetic counselors and other genetics providers. This study demonstrated the range of emotional responses adult undiagnosed patients may have from receiving a clinically uncertain exome sequencing result, from disappointment and frustration to happiness and relief, and many felt more than one of these emotions at the same time. Genetic counselors should remain prepared to help clients process the variety of emotions they may feel during result disclosure. Our results suggest that the chronic uncertainty of a diagnostic odyssey may contribute to adult patients with undiagnosed conditions being better prepared for coping with and adapting to the additional uncertainty from their clinically uncertain result from exome sequencing. However, continuing to set expectations about the larger likelihood of receiving a clinically uncertain result from exome sequencing during pre-test counseling is still important. The increasing demand for genetic counseling services may result in changes to genetic counseling practice that may eliminate or alter pre-test counseling, yet such changes should still incorporate expectation-setting.

Adult patients with undiagnosed conditions conceptualize the uncertainty of their result in a variety of ways. Genetic counselors should explore the ways in which their clients perceive this uncertainty to facilitate appropriate meaning-making of their result. Assessing the client's prior beliefs for the cause of the undiagnosed condition and eliciting the experience of their diagnostic odyssey may also help in this process, especially if these conversations occur during pre-test counseling.

Reanalysis was acknowledged by participants as an important benefit of undergoing exome sequencing and was a source of hope. Many participants understood the opportunity for reanalysis of their exome sequencing results or genomic data and maintained the hope that technologic advances would someday discover the cause of their condition. The process of exome sequencing reanalysis is not always automated or guaranteed by genetics clinics or laboratories

and is often initiated differently depending on the clinic. Sometimes, clinics will only facilitate reanalysis if prompted by the patient through a phone call or follow-up visit. Other times, genetic counselors or laboratories will initiate reanalysis after a certain number of years have passed after initial result disclosure. Regardless, reanalysis requires additional work by genetic counselors or the laboratories that conducted the exome sequencing. Genetic counselors must re-contact laboratories that do not conduct reanalysis automatically to initiate the process. For genetic counselors who partner with laboratories that do not offer reanalysis, they must re-interpret exome sequencing results themselves through searches through the literature and genomic databases. Reanalysis is an important practice for patients and providers because it may provide diagnoses for patients and works to expand the knowledge of genomics. Providers and laboratories should do what they can to facilitate reanalysis for their patients and overall practice. As exome sequencing becomes more broadly available, genetics clinics and laboratories should consider developing systematic plans for conducting reanalysis for all patients who consent to it. The process may become more easily automated with the development of reanalysis functionalities of genomic databases.

Many participants mentioned that they would like to participate in support groups or research studies but are unable to find opportunities for which they qualify or fit in. While most research opportunities require a diagnosis to qualify for participation, providers may be equipped with referrals to research studies like ours, which focus on undiagnosed patient populations. In addition, genetic counselors may consider developing and/or facilitating support groups for their undiagnosed patients within their clinical centers. They may also offer to connect their undiagnosed patients who express a desire to speak with others who are undiagnosed.

The purpose of this study was to provide a preliminary understanding of how adult undiagnosed patients recall, perceive, and cope with the uncertainty from a clinically uncertain exome sequencing results. This patient population and their responses to genomic uncertainty

remain ripe for future studies. Larger-scale quantitative studies on the affective and behavioral impacts of clinically uncertain exome sequencing results may provide more generalizable information and target specific challenges in coping and adapting to these results that may inform intervention studies. As exome sequencing is offered earlier in the diagnostic process for individuals in the future, comparative studies about reactions to clinically uncertain results in adult patient populations may be warranted. Future studies may also include topics such as the impact of other less common types of clinically uncertain exome sequencing results on adult undiagnosed patients, as well as the typical practices of genetic counselors in providing pre- and post-test genetic counseling to adult undiagnosed patients seeking exome sequencing and receiving clinically uncertain results.

Appendix A: *A Taxonomy of Medical Uncertainties in Clinical Genome Sequencing*

I. Sources
   a. Probability: the indeterminacy or lack of predictability of a phenomenon
   b. Ambiguity: the lack of reliability, credibility, or adequacy of information about a phenomenon
      i. Conceptual
         1. Model inadequacy: Limitations in the adequacy of models, both theoretical (e.g., gene models) or empirical (e.g., animal system models), to represent gene-disease mechanisms in humans.
         2. Nosologic inadequacy: Limitations in the adequacy of current disease or phenotype classifications.
      ii. Methodological
         1. Sample or data integrity problems: Limitations in laboratory samples or processing techniques resulting in diagnostic error.
         2. Test limitations: Inherent constraints in the accuracy or precision of laboratory instrumentation or techniques.
         3. Unmeasured factors: Biological factors that affect the phenotype but are as yet undiscovered or not assayed.
         4. Procedural variability or error: An attribute that is subject to random variation that leaves a variant undetected.
         5. Test misinterpretation: Failure of diagnostic personnel to correctly annotate or interpret a result.
      iii. Clinical
         1. Incomplete or conflicting data: Gaps or inconsistencies in family history, pedigree, and clinical outcomes.
   c. Complexity: aspects of a phenomenon that make it difficult to analyze or comprehend
      i. Multiplicity of Causes
         1. Locus heterogeneity: A single disorder or phenotypic characteristic that can be caused by gene mutations in heterogeneous genes (e.g., autism).
         2. Complex genetic traits: A single disorder or phenotypic characteristic that is determined in a single individual by variation at multiple genetic loci (e.g., height)
         3. Non-genetic causation: Non-genetic (i.e., environmental) determinants of disorders or phenotypic characteristics, which may interact with genetic determinants and often have poorly quantified effects.
      ii. Multiplicity of Effects
         1. Pleiotropy: A single gene mutation that causes multiple apparently unrelated disorders or phenotypic characteristics.
      iii. Effect modification (moderating, mediating pathways)

1. Gene x Environment Interactions: Whether environmental factors will exacerbate or ameliorate manifestations of disease.

II. Issues
    a. Scientific: data-centered issues
        i. Diagnostic: Unknown condition or risk.
            1. Gene-Phenotype Association: The likelihood that deleterious variants in this gene actually cause disease.
            2. Pathogenicity of Variants
            3. Phenotype-Disease Association: The likelihood that a given phenotypic manifestation is part of a disease or syndrome.
        ii. Prognostic: Which disease manifestations will or will not arise, how they are likely to evolve over time, the rate and tempo of disease.
            1. Individual
            2. Family
        iii. Causal: Underlying factors and mechanisms that determine or explain a given genomic variant or its ultimate phenotype.
        iv. Therapeutic: Unknown approach to treatment or prevention of disease or risk.
            1. Prevention
            2. Treatment
    b. Personal: person-centered issues
        i. Psychological
        ii. Social
        iii. Financial
        iv. Existential
    c. Practical: systems-centered issues
        i. Structural: Limitations in institutional facilities and resources
            1. Facilities for participating in genomic testing
            2. Facilities for participating in research
        ii. Procedural: Limitations of actions required to access and utilize health care services
            1. Genomic testing
            2. Research
            3. Policy development and implementation

III. Locus
    a. Patient/participant/family
    b. Lab personnel
    c. Clinician
    d. Investigator
    e. Policymaker

Appendix B: Recruitment Script for Genetic Counselors

Email/Electronic Medical Records Format:

Hello *(name of participant),*

This is *(name of genetic counselor),* your genetic counselor from *(name of clinic)* who provided you with a genetic test called exome sequencing back in *(year of exome sequencing result disclosure)*. I am contacting you because we have a Masters student, Ahna Neustadt, who is interested in interviewing you over the phone for her thesis project. She is doing a project about how people like you have experienced receiving exome sequencing test results.

Ahna would like to contact you to tell you more about her project and how you can participate. If you would like for Ahna to contact you, you would need to provide permission for me to give her your name, email address, phone number, and current mailing address. After talking with Ahna, you can decide whether or not you want to participate in her study. You would receive a $20 gift card after participating in the research project if you decide to take part.

Please respond to this message stating whether you give me permission to give Ahna your name and contact information.

Thank you for your consideration!

Best,
name of genetic counselor

Phone Call Format:

Hi! This is *(name of genetic counselor)* from *(name of clinic).* I am calling for *(name of participant),* is this he/she?

Hi, *(name of participant).* I am your genetic counselor who provided you with a genetic test called exome sequencing back in *(year of exome sequencing result disclosure)*. I am calling you because we have a Masters student, Ahna Neustadt, who is interested in interviewing you over the phone for her thesis project. She is doing a project about how people like you have experienced receiving exome sequencing test results.

Ahna would like to contact you to tell you more about her project and how you can participate. If you would like for Ahna to contact you, you would need to provide permission for me to give her your name, email address, phone number, and current mailing address. After talking with Ahna, you can decide whether or not you want to participate in her study. You would receive a $20 gift card after participating in the research project if you decide to take part.

Are you interested in Ahna contacting you for her research project?

> If they say no: No problem. Thank you for consideration. Have a wonderful day! Bye.
>
> If they say yes: Great! You just need to provide me with verbal permission for me to give her your contact information.

(Participant provides verbal confirmation…) Thank you. I will note your permission in your records and Ahna will contact you soon. Have a wonderful day! Bye.

Appendix C: Recruitment Letter - Kennedy Krieger Institute

Dear _____,

You are invited to participate in a study conducted by researchers at the National Human Genome Research Institute and Johns Hopkins School of Public Health. A main goal of our research is to understand how people think, feel, and act after receiving different kinds of genetic test results. We are especially interested in understanding how people react to getting these kinds of results as part of a search for a diagnosis. You are being contacted because you have had a genetic test called an exome sequence through Kennedy Krieger Institute.

We currently know little about how people react to getting different kinds of genetic test results from exome sequencing. The information gained from this study will provide a deeper understanding of this experience. In addition, we hope that this study will inform how genetic counselors talk about results with their patients. We also hope that it will help genetic counselors better understand how to help patients like you cope with their results.

This study involves a 45-60 minute phone interview and the completion of 2 short surveys before the interview. During the interview, you will be asked questions about your test result. We will also ask you to respond to some general questions about yourself. People who take part in this study will receive a $20 gift card as payment for their time.

You may take part in this study if you meet the following:
1. You were 18 years or older at the time you received your exome sequence test results
2. You are able to speak and understand English
3. You are able to consent for yourself and participate in a phone interview

If you are willing to take part in this study or are interested in receiving more information about this study please contact the researchers below by phone or email. If you would prefer that we not contact you further, please let us know. We have tried to reach you by phone but have not been successful. We will continue to try to reach you by phone if we do not hear directly from you. Thank you for your time and consideration. We look forward to learning from your answers in the future.

Sincerely,

Ahna Neustadt, BS
Graduate Student,
Genetic Counseling Training Program
Johns Hopkins University/NHGRI
Baltimore, MD
Phone: 301-827-5031
Email: ahna.neustadt@nih.gov

Lori Erby, PhD, ScM, CGC
Director, JHU/NHGRI GCTP Training Program
Adjunct Asst. Prof., Dpt. of Health, Behavior & Society
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
Phone: 301-443-2635
Email: lori.erby@nih.gov

Appendix D: Recruitment Letter - Johns Hopkins Hospital Genetics Clinics

Dear _____,

You are invited to participate in a study conducted by researchers at the National Human Genome Research Institute and Johns Hopkins School of Public Health. A main goal of our research is to understand how people think, feel, and act after receiving different kinds of genetic test results. We are especially interested in understanding how people react to getting these kinds of results as part of a search for a diagnosis. You are being contacted because you have had a genetic test called an exome sequence through Johns Hopkins Hospital Genetics Clinic.

We currently know little about how people react to getting different kinds of genetic test results from exome sequencing. The information gained from this study will provide a deeper understanding of this experience. In addition, we hope that this study will inform how genetic counselors talk about results with their patients. We also hope that it will help genetic counselors better understand how to help patients like you cope with their results.

This study involves a 45-60 minute phone interview and the completion of 2 short surveys before the interview. During the interview, you will be asked questions about your test result. We will also ask you to respond to some general questions about yourself. People who take part in this study will receive a $20 gift card as payment for their time.

You may take part in this study if you meet the following:
1. You were 18 years or older at the time you received your exome sequence test results
2. You are able to speak and understand English
3. You are able to consent for yourself and participate in a phone interview

If you are willing to take part in this study or are interested in receiving more information about this study please contact the researchers below by phone or email. If you would prefer that we not contact you further, please let us know. We have tried to reach you by phone but have not been successful. We will continue to try to reach you by phone if we do not hear directly from you. Thank you for your time and consideration. We look forward to learning from your answers in the future.

Sincerely,

Ahna Neustadt, BS
Graduate Student,
Genetic Counseling Training Program
Johns Hopkins University/NHGRI
Baltimore, MD
Phone: 301-827-5031
Email: ahna.neustadt@nih.gov

Lori Erby, PhD, ScM, CGC
Director, JHU/NHGRI GCTP Training Program
Adjunct Asst. Prof., Dpt. of Health, Behavior & Society
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
Phone: 301-443-2635
Email: lori.erby@nih.gov

Appendix E: Script for Recruitment Phone Calls

Hello. I am calling for (name of participant). Am I speaking with the correct person?

Hi, my name is Ahna Neustadt. I am a graduate student from Johns Hopkins and I am conducting research for my master's thesis. Your genetic counselor from (clinic name) has acquired permission from you that I may contact you for my research. I would like to tell you about my research project because you are eligible to participate. Are you interested in hearing about my study and what your participation would involve?

If they say they are not interested: *Okay that is fine. Thank you for your consideration!*

If they say they are interested: *Great! I'm happy to hear you are interested in hearing more. My study is about how people who are seeking a diagnosis respond to genetic testing results from a test called exome sequencing. Your genetic counselor informed my research team that you received exome sequencing from (clinic name) as a way to try to get a diagnosis for a health condition. We are curious to learn about your experience receiving your genetic test result and how this result has influenced how you think about your health. Your participation in the study would require a 45-60 minute phone interview and completing a short survey from home before the interview. After the interview you will be mailed a $20 gift card for your time. Does this sound like something you would like to participate in?*

If they say no: *Okay that is fine. Thank you for your consideration!*

If they say yes: *Wonderful! I will go ahead and send you a consent form, which will explain more details about the project and what your participation would involve. Would you prefer I send this to you by mail or email?*

Please review the consent form and contact me at any time if you have questions about it or the research project. You will find my contact information at the end of the consent form. If you agree with the terms on the consent form and would like to participate in the phone interview, you will need to sign the consent form and send it back to me before your interview date. You can send it to me by mail, email, fax, whatever method is most preferable to you. Let's go ahead and schedule a date now for your phone interview.

What phone number would you like me to call for the phone interview?

Also, along with the consent form, I will be sending you two short surveys to fill out. Please fill these out before your interview date. You do not need to return these back to me. Instead, hold on to them and on our interview date, I will collect your answers to these surveys verbally before we begin the interview.

Do you have any further questions?

I look forward to our phone interview on (date /time scheduled). Thank you!

Follow-Up Phone Call

Hello. I am calling for (name of participant). Am I speaking with the correct person?

Hi, my name is Ahna Neustadt. I am a graduate student from Johns Hopkins and I am conducting research for my master's thesis. I am calling about the research project about genetic testing that you should have received a recruitment letter for. I was wondering if you received this recruitment letter?

If they say they did not receive the recruitment letter: *I see. Well I'd like to tell you a bit about this study that you are eligible to participate in if you have a moment?*

If they say they are not interested: *Okay that is fine. Thank you for your consideration!*

If they say they are interested: *Great! I'm happy to hear you are interested in hearing more. The study is about how people who are seeking a diagnosis respond to genetic testing results from a test called exome sequencing. Your genetic counselor informed my research team that you received exome sequencing from (clinic name) as a way to try to get a diagnosis for a health condition. We are curious to learn about your experience receiving your genetic test result and how this result has influenced how you think about your health. Your participation in the study would require a 45-60 minute phone interview and completing a short survey from home before the interview. After the interview you will be mailed a $20 gift card for your time. Does this sound like something you would like to participate in?*

If they say no: *Okay that is fine. Thank you for your consideration!*

If they say yes: *Wonderful! I will go ahead and send you a consent form, which will explain more details about the project and what your participation would involve. Would you prefer I send this to you by mail or email?*

Please review the consent form and contact me at any time if you have questions about it or the research project. You will find my contact information at the end of the consent form. If you agree with the terms on the consent form and would like to participate in the phone interview, you will need to sign the consent form and send it back to me before your interview date. You can send it to me by mail, email, fax, whatever method is most preferable to you. Let's go ahead and schedule a date now for your phone interview.

What phone number would you like me to call for the phone interview?

Also, along with the consent form, I will be sending you two short surveys to fill out. Please fill these out before your interview date. You do not need to return these back to me. Instead, hold on to them and on our interview date I will collect your answers to these surveys verbally before we begin the interview.

Do you have any further questions?

I look forward to our phone interview on (date /time scheduled). Thank you!

If they say they did receive the recruitment letter: *Oh good I'm glad you received it. Since I haven't heard back from you in a few weeks since I sent out the recruitment letter, I was wondering whether you are interested in hearing more or thinking about participating in the research project?*

If they say they are not interested: *Okay that is fine. Thank you for your consideration!*

If they say they are interested: *Great! I'm happy to hear you are interested in hearing more. The study is about how people who are seeking a diagnosis respond to genetic testing results from a test called exome sequencing. Your genetic counselor informed my research team that you received exome sequencing from (clinic name) as a way to try to get a diagnosis for a health condition. We are curious to learn about your experience receiving your genetic test result and how this result has influenced how you think about your health. Your participation in the study would require a 45-60 minute phone interview and completing a short survey from home before the interview. After the interview you will be mailed a $20 gift card for your time. Does this sound like something you would like to participate in?*

If they say no: *Okay that is fine. Thank you for your consideration!*

If they say yes: *Wonderful! I will go ahead and send you a consent form, which will explain more details about the project and what your participation would involve. Would you prefer I send this to you by mail or email?*

Please review the consent form and contact me at any time if you have questions about it or the research project. You will find my contact information at the end of the consent form. If you agree with the terms on the consent form and would like to participate in the phone interview, you will need to sign the consent form and send it back to me before your interview date. You can send it to me by mail, email, fax, whatever method is most preferable to you. Let's go ahead and schedule a date now for your phone interview.

What phone number would you like me to call for the phone interview?

Also, along with the consent form, I will be sending you two short surveys to fill out. Please fill these out before your interview date. You do not need to return these back to me. Instead, hold on to them and on our interview date I will collect your answers to these surveys verbally before we begin the interview.

Do you have any further questions?

I look forward to our phone interview on (date/time scheduled). Thank you!

Appendix F: Consent Form - Kennedy Krieger Institute

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
INFORMED CONSENT FOR ADULT PARTICIPANTS

Study Title: Adult Patients with Undiagnosed Conditions and their Responses to Clinically Uncertain Results from Exome Sequencing

Principal Investigator: Jill Owczarzak
IRB No.: IRB00008725
PI Version Date: Version 3; 5/8/18

What you should know about this study

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- You are a volunteer. You may choose not to take part at all, and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.

Purpose of research project

This research is being done to understand how people think, feel, and act after receiving their genetic test results.

Why we are asking you to participate

You are being asked to participate because you have had a genetic test called an exome sequence through Kennedy Krieger Institute. We are interested in hearing from about 40 people who have received different kinds of results from the genetic test called exome sequencing. You can take part in this study if you were 18 years or older at the time you received your test result, and if you are English speaking.

Study procedures

You will be asked to take part in a 45-60 minute interview on the telephone, as well as fill out 2 short surveys before the interview. We will audio record the interview, and it will later be transcribed. The interview will ask you some questions about what led up to the exome sequencing test and what your reactions were like when you got your test result. You will also be asked to answer several general questions about yourself.

Risks/Discomforts

There are no physical risks of taking part in this study. However, it is possible that some questions may make you feel upset or anxious. If partaking in the interview makes you feel upset you can stop the interview at any point or skip any questions you do not wish to answer. If you feel upset after completing the interview or have any additional concerns, you may contact the researchers using the information provided below. Talking about your test result may also raise some questions for you. If that happens, we will refer you to someone who may be able to answer those questions.

Benefits

You are not expected to benefit directly from taking part in this study. The information you provide may help to improve our understanding of what it is like for individuals to get different kinds of genetic test results from exome sequencing. We hope that this will help genetic counselors improve how they talk about results with their patients. We also hope that it will help genetic counselors better understand how to help patients like you cope with these types of results.

Payment

You will receive a $20 gift card for participating in the study. If you choose to quit the study early, you will only receive the $20 gift card if you complete at least half of the interview.

Data Sharing and Confidentiality

Any personal information that you provide to us will be stored in a private and confidential manner. Your name and contact information will be linked with an ID number, and the ID number will be linked to information about you and your interview. The file that links your name to your ID number and contact information will be kept in a secure and password-controlled location. Everything will be labeled only with your ID number. Once we have finished your interview, we will delete the file with your name and contact information. Your responses will not be part of any medical record. When we report our research results, it will be done without identifiable information from individual people. If you mention any specific names during your interview, we will not transfer any of their personal information, including their names, into the transcript.

Protecting your privacy during data collection

Interviews will take place over the phone. To ensure your privacy, please make sure that the location you choose to be in during your phone interview is private enough. We recommend you avoid public spaces during your phone interview.

What happens if you leave the study early?

If partaking in the interview makes you feel upset you can stop the interview at any point or skip any questions you do not wish to answer. If you choose to stop the interview, you can decide whether or not you would like the parts of the interview you finished to be included in the study.

Authorization for Disclosure of Protected Health Information for Research

We are asking you to authorize the disclosure and use of your private health information for this research study. By signing this authorization, you agree that Kennedy Krieger Institute may release your private health information to us for use in this research study.

Your private health information that we may use for this research includes:

- Category of result from exome sequencing (either variant of unknown significance or negative - but **not** information about the specific genetic change).
- Number of days between the date you elected exome sequencing and the date you received your genetic test results.
- Approximate date you received your exome sequencing result (only month and year).
- Whether or not you have received a diagnosis since getting exome sequencing (yes or no).
- Your personal description of your medical condition that you provide during your telephone interview.

The people who may receive or use your private health information include the researchers and their staff.

Kennedy Krieger Institute is required by the Federal Privacy Rule to protect your private health information. By signing this Authorization, you permit them to release your information to the researchers for use in this research study. The researchers will try to make sure that everyone who needs to see your private information for this research keeps it confidential, but we cannot guarantee this. Although the researchers may not be covered by the Federal Privacy Rule, they will make an effort to protect your information using the same standards.

Some other people may see your private health information outside of the research team. They may include the sponsor of the study, study safety monitors, government regulators, and legal compliance staff. All these people must also keep your information confidential.

You do not have to sign this Authorization, but otherwise you may not join the study. It is your choice.

Your Authorization does not have an expiration date; it will continue as long as the research continues. You may change your mind and take back this Authorization at any time. If you take it back, the researchers may still use the private health information they have collected about you to that point. To take back the Authorization, you must contact the researcher.

Who do I call if I have questions or problems?

- Call the senior investigator, Lori Erby, at 301-443-2635 if you have questions or complaints. You may also call the student investigator, Ahna Neustadt, at 301-827-5031.

- Call or contact the **Johns Hopkins Bloomberg School of Public Health IRB Office** if you have questions about your rights as a participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

  Address: Johns Hopkins Bloomberg School of Public Health
  615 N. Wolfe Street, Suite E1100, Baltimore, MD 21205

  Telephone: 410-955-3193; Toll Free: 1-888-262-3242
  E-mail: jhsph.irboffice@jhu.edu

What does your signature on this consent form mean?

Your signature on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____	_____	_____
Print name of Adult Participant	Signature of Adult Participant	Date

_____	_____	_____
Print name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

☐ ***Please check the box ONLY if you prefer your phone interview to NOT be audio-recorded. If you check this box, we will make sure there is a note-taker present during your interview instead.***

Please send your signed consent form to the student investigator, Ahna Neustadt. You can return this in one of the following ways:

- **Email: ahna.neustadt@nih.gov**
- **Mail: Ahna Neustadt**
  31 Center Dr
  B1B36
  Bethesda, MD 20892

- **Fax: 301-480-3108**

Appendix G: Consent Form - Johns Hopkins Hospital Genetics Clinics

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
INFORMED CONSENT FOR ADULT PARTICIPANTS

Study Title: Adult Patients with Undiagnosed Conditions and their Responses to Clinically Uncertain Results from Exome Sequencing

Principal Investigator: Jill Owczarzak
IRB No.: IRB00008725
PI Version Date: Version 3; 5/8/18

What you should know about this study

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- You are a volunteer. You may choose not to take part at all, and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.

Purpose of research project

This research is being done to understand how people think, feel, and act after receiving their genetic test results.

Why we are asking you to participate

You are being asked to participate because you have had a genetic test called an exome sequence through Johns Hopkins Hospital Genetics Clinic. We are interested in hearing from about 40 people who have received different kinds of results from the genetic test called exome sequencing. You can take part in this study if you were 18 years or older at the time you received your test result, and if you are English speaking.

Study procedures

You will be asked to take part in a 45-60 minute interview on the telephone, as well as fill out 2 short surveys before the interview. We will audio record the interview, and it will later be transcribed. The interview will ask you some questions about what led up to the exome sequencing test and what your reactions were like when you got your test result. You will also be asked to answer several general questions about yourself.

Risks/Discomforts

There are no physical risks of taking part in this study. However, it is possible that some questions may make you feel upset or anxious. If partaking in the interview makes you feel upset you can stop the interview at any point or skip any questions you do not wish to answer. If you feel upset after completing the interview or have any additional concerns, you may contact the researchers using the information provided below. Talking about your test result may also raise some questions for you. If that happens, we will refer you to someone who may be able to answer those questions.

Benefits

You are not expected to benefit directly from taking part in this study. The information you provide may help to improve our understanding of what it is like for individuals to get different kinds of genetic test results from exome sequencing. We hope that this will help genetic counselors improve how they talk about results with their patients. We also hope that it will help genetic counselors better understand how to help patients like you cope with these types of results.

Payment

You will receive a $20 gift card for participating in the study. If you choose to quit the study early, you will only receive the $20 gift card if you complete at least half of the interview.

Data Sharing and Confidentiality

Any personal information that you provide to us will be stored in a private and confidential manner. Your name and contact information will be linked with an ID number, and the ID number will be linked to information about you and your interview. The file that links your name to your ID number and contact information will be kept in a secure and password-controlled location. Everything will be labeled only with your ID number. Once we have finished your interview, we will delete the file with your name and contact information. Your responses will not be part of any medical record. When we report our research results, it will be done without identifiable information from individual people. If you mention any specific names during your interview, we will not transfer any of their personal information, including their names, into the transcript.

Protecting your privacy during data collection

Interviews will take place over the phone. To ensure your privacy, please make sure that the location you choose to be in during your phone interview is private enough. We recommend you avoid public spaces during your phone interview.

What happens if you leave the study early?

If partaking in the interview makes you feel upset you can stop the interview at any point or skip any questions you do not wish to answer. If you choose to stop the interview, you can decide whether or not you would like the parts of the interview you finished to be included in the study.

Authorization for Disclosure of Protected Health Information for Research

We are asking you to authorize the disclosure and use of your private health information for this research study. By signing this authorization, you agree that Johns Hopkins Hospital Genetics Clinic may release your private health information to us for use in this research study.

Your private health information that we may use for this research includes:

- Category of result from exome sequencing (either variant of unknown significance or negative - but **not** information about the specific genetic change).
- Number of days between the date you elected exome sequencing and the date you received your genetic test results.
- Approximate date you received your exome sequencing result (only month and year).
- Whether or not you have received a diagnosis since getting exome sequencing (yes or no).
- Your personal description of your medical condition that you provide during your telephone interview.

The people who may receive or use your private health information include the researchers and their staff.

Johns Hopkins Hospital Genetics Clinic is required by the Federal Privacy Rule to protect your private health information. By signing this Authorization, you permit them to release your information to the researchers for use in this research study. The researchers will try to make sure that everyone who needs to see your private information for this research keeps it confidential, but we cannot guarantee this. Although the researchers may not be covered by the Federal Privacy Rule, they will make an effort to protect your information using the same standards.

Some other people may see your private health information outside of the research team. They may include the sponsor of the study, study safety monitors, government regulators, and legal compliance staff. All these people must also keep your information confidential.

You do not have to sign this Authorization, but otherwise you may not join the study. It is your choice.

Your Authorization does not have an expiration date; it will continue as long as the research continues. You may change your mind and take back this Authorization at any time. If you take it back, the researchers may still use the private health information they have collected about you to that point. To take back the Authorization, you must contact the researcher.

Who do I call if I have questions or problems?

- Call the senior investigator, Lori Erby, at 301-443-2635 if you have questions or complaints. You may also call the student investigator, Ahna Neustadt, at 301-827-5031.

- Call or contact the **Johns Hopkins Bloomberg School of Public Health IRB Office** if you have questions about your rights as a participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

  Address: Johns Hopkins Bloomberg School of Public Health
  615 N. Wolfe Street, Suite E1100, Baltimore, MD 21205

  Telephone: 410-955-3193; Toll Free: 1-888-262-3242
  E-mail: jhsph.irboffice@jhu.edu

What does your signature on this consent form mean?

Your signature on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____	_____	_____
Print name of Adult Participant	Signature of Adult Participant	Date
_____	_____	_____
Print name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

☐ ***Please check the box ONLY if you prefer your phone interview to NOT be audio-recorded. If you check this box, we will make sure there is a note-taker present during your interview instead.***

Please send your signed consent form to the student investigator, Ahna Neustadt. You can return this in one of the following ways:

- **Email: ahna.neustadt@nih.gov**
- **Mail: Ahna Neustadt**
  31 Center Dr
  B1B36
  Bethesda, MD 20892

- **Fax: 301-480-3108**

Appendix H: Intolerance of Uncertainty Short Form Scale

Below are questions that help researchers understand how much an individual tolerates uncertainty. Before your scheduled interview, please take time to answer these questions and record your answers on this sheet. Before the researcher begins to ask interview questions, she will have you verbally report your answers to these questions on the phone. Your answers will be recorded and anonymized.

Please circle the number that best corresponds to how much you agree with each item.

	Not at all characteristic of me	A little characteristic of me	Somewhat characteristic of me	Very characteristic of me	Entirely characteristic of me
1. Unforeseen events upset me greatly.	1	2	3	4	5
2. It frustrates me not having all the information I need.	1	2	3	4	5
3. Uncertainty keeps me from living a full life.	1	2	3	4	5
4. One should always look ahead so as to avoid surprises.	1	2	3	4	5
5. A small unforeseen event can spoil everything, even with the best of planning.	1	2	3	4	5
6. When it's time to act, uncertainty paralyses me.	1	2	3	4	5
7. When I am uncertain I can't function very well.	1	2	3	4	5
8. I always want to know what the future has in store for me.	1	2	3	4	5
9. I can't stand being taken by surprise.	1	2	3	4	5
10. The smallest doubt can stop me from acting.	1	2	3	4	5
11. I should be able to organize everything in advance.	1	2	3	4	5
12. I must get away from all uncertain situations.	1	2	3	4	5

Appendix I: Perceptions of Uncertainties in Genome Sequencing Scale

Below are questions that help researchers understand how an individual feels about exome sequencing. Before your scheduled interview, please take time to answer these questions and record your answers on this sheet. Before the researcher begins to ask interview questions, she will have you verbally report your answers to these questions on the phone. Your answers will be recorded and anonymized.

Perceptions of Uncertainties in Genome Sequencing (PUGS)

Rate how certain you feel about the following aspects of your sequence results:

	Very Uncertain				Very Certain
1. What my test results may mean for my health	1	2	3	4	5
2. What future actions I will need to take based on my test results	1	2	3	4	5
3. Whether to discuss my test results with my non-genetics physician	1	2	3	4	5
4. How my physician may use my results to improve my health	1	2	3	4	5
5. Whether I am worried or concerned about my test results	1	2	3	4	5
6. Whether my test results reveal something alarming	1	2	3	4	5
7. Whether I am reassured or encouraged by my test results	1	2	3	4	5
8. Whether my test results may disrupt my life	1	2	3	4	5
9. Whether I am able to trust my test results	1	2	3	4	5
10. Whether my test results are accurate	1	2	3	4	5

Appendix J: Interview Guide

Are you in a place that you feel is private enough to have this interview?

Now that we have finished the informed consent process, I would like to ask you a few questions to collect demographic information about you:

1) Would you describe your ethnicity as:
- *Hispanic or Latino*
- *Not Hispanic or Latino*

2) Which one or more categories describes your race?
- *American Indian or Alaska Native*
- *Asian*
- *Black or African American*
- *Native Hawaiian or Other Pacific Islander*
- *White*
- *Other: _____*

2) What level of education have you currently completed?
- *Graduate School*
- *College Graduate*
- *Some College*
- *High School*
- *Some High School or less*

3) What is your estimated annual household income?
- *<$45,000*
- *$45,000–$89,999*
- *≥ $90,000*

4) How long have you been seeking a diagnosis for your condition?
- *6 months-1 year*
- *1-2 years*
- *2-3 years*
- *3-4 years*
- *5-10 years*
- *over 10 years*

Thank you! Now I need to quickly collect your responses to the 2 short surveys I sent you. Do you have these answers ready to read aloud to me?

> Response 1: *Great! I'll go over each question and you tell me the number that you selected for your answer.*
> Response 2: *Oh, you haven't completed the surveys yet. Alright, well let's complete it together now then. I'll go over each question and you can tell me the number you select as your answer.*

Now we'll begin the interview. As a reminder, it's ok to mention any provider, family or friend's name as they will not be transcribed for the study. During our conversation, I would like you to focus on the experience of receiving your genetic test result and how this result has affected you.

Although we'll primarily talk about your testing experience, first tell me a bit about your experience with trying to find a diagnosis before you had the exome sequencing test. (Prompt if necessary: Focus on aspects of uncertainty related to this experience.)

- PROMPT: Before getting exome sequencing, did you have any ideas about what was causing your symptoms/condition? If so, what were your ideas about this?
- Can you briefly describe your symptoms?

Thank you. Now, let's talk about what led to you to decide to seek genetic testing for your undiagnosed condition.

- What led you to get exome sequencing at (*insert clinic name*)?
    - PROMPT:
        - Had you heard about exome sequencing before your visit at (*insert clinic name*)? If so, what did you already know about exome sequencing? Where did you learn this information?
        - Did your prior knowledge influence your decision to pursue exome sequencing? In what ways?
            - What were reasons you might have wanted exome sequencing?
            - Were there any reasons why you were unsure?

Now I'd like to ask you about your test result and your experiences on the day you received your test result.

- Who told you about your result?
- Was it in person or over the phone?
- Was there anyone else with you when you learned about your result? If so, who were they?

- What did the *(insert response about who told the results)* say to you about your exome sequencing result?
    - PROMPTS:
        - Do you remember what they called the type of result?
        - What did they say about it being or not being the cause of your symptoms/condition?
        - Did they say the result would have any medical consequences for your family members?

- Did the information the *(insert response about who told the results)* tell you make sense at the time you were first hearing it?
    - PROMPTS:
        - What made sense and what did not make sense?
        - What kinds of questions did you ask?

- Did the information the *(insert response about who told the results)* tell you meet your hopes and expectations?
    - PROMPTS:
        - What did you expect to learn from exome sequencing?
            - Did you expect to get a diagnosis?
            - What different kinds of results did you understand were possible to get from exome sequencing?
        - What were you hoping the results would be?
        - How confident were you that exome sequencing would provide a diagnosis?
        - How did exome sequencing compare to other genetic tests you had previously?

- Did you seek additional information after your meeting with *(insert response about who told the results)?* If so, what additional information were you looking for? What did you do to learn more?

Now I'd like to ask you about how you reacted after receiving this test result.

- What thoughts ran through your mind when you first learned about your result?
    - PROMPTS:
        - Did the result make you think differently about the cause of your symptoms/condition? If so, in what ways?
        - Did you react the way you expected to?
        - How would you describe your emotions in that moment?

- Have you told anyone about your result? If so, who did you talk to?
    - PROMPTS: Healthcare providers? Family members? Friends?
- What did you tell them?
    - PROMPTS:
        - Why did you choose to tell the people you did?
        - Was there anyone that you specifically chose not to tell? If so, why did you choose not to tell them?

- Has receiving your exome results influenced you to take any actions?
    - PROMPTS:
        - Have you sought additional testing/second opinion? If so, why? Did you learn anything new or different?
        - Have you sought additional or new medical care? If yes, please explain the types of care you have sought and why. If no, explain why you have not sought new care.
        - Have you chosen to participate in any research related to your result or your symptoms/condition? If yes, please explain the type of research you have participated in and why.

        - Have you joined any support groups? If yes, please explain the type(s) of support group(s) you have joined and why.
        - Have you participated in advocacy activities related to your result or your symptoms/condition? If yes, please explain the types of advocacy activities you have participated in and why.

- Does the way you feel about your exome sequencing result today differ from the way you felt about it after first hearing about it? If so, how are your feelings different?
    - PROMPTS:
        - Have your thoughts about your result in relation to your symptoms/condition changed overtime?
        - What has contributed to you feeling differently?

- Overall, how do you think you have dealt with knowing your result? What do you do to cope?
    - PROMPTS:
        - (if they have described their result as uncertain): How do you cope with the uncertainty of your result?
- What has been most difficult for you about receiving your result? What has been most helpful?

- At this current time (if still undiagnosed):
    - Is there still additional information you feel like you need to help you make sense of your result?
    - Do you expect to hear from someone again about your genetic test result? If so, when and why?
    - If new information became available about your result would you want to learn about it? Why?
- At this current time (if since been diagnosed):
    - What tests have you had after exome sequencing that have given you further information about your symptoms/conditions (provided you with a diagnosis)?

We've come to the end of the interview. I want to thank you again for agreeing to participate. Before we wrap up, are there any questions you have for me? Is there anything you were expecting me to ask or were hoping to talk about that didn't come up?

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CURRICULUM VITAE

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EDUCATION

ScM, Genetic Counseling .....……..January 2019
Johns Hopkins University/National Human Genome Research Institute Genetic Counseling Training Program (JHU/NHGRI GCTP)

B.S., Biochemistry & Cell Biology……..…….June 2014
University of California, San Diego (UCSD)
Cum Laude Honors, Warren College Honors, Warren College Provost's Honors

GENETIC COUNSELING TRAINEE

Clinical Rotation Sites
Johns Hopkins Cancer Genetics Clinic, 70 hrs……..Oct.-Dec. 2018
Kennedy Krieger Institute, 100 hrs……Aug.-Oct. 2018
National Eye Institute, NIH, 100 hrs……..March-Aug. 2018
Mercy Hospital, Center for Advanced Fetal Care, 70 hrs…….....Oct.-Dec. 2017
ClinSeq Project, NHGRI, 50 hrs……Aug.-Oct. 2017
Cancer Center of Santa Barbara at Sansum Clinic, 160 hrs…….....July-Aug. 2017
Johns Hopkins DNA Diagnostics Lab, 70 hrs...…….March-May 2017
Greater Washington Maternal Fetal Medicine, 70 hrs…….Jan.-March 2017
Johns Hopkins Pediatrics/General Genetics Clinic, 65 hrs……Oct.-Dec. 2016

COUNSELING EXPERIENCE

Intern Counselor…… Feb. 2015-June 2016
BreakThrough Student Assistance Program, Thousand Oaks, CA
Supervisor: Kathleen Murvin, M.A.

Shadowing Prenatal Genetic Counselor, 55 hrs ……....Jan. 2015-Oct. 2015
Providence Holy Cross Medical Center, Mission Hills, CA
Genetic Counselor: Francesca Morris, MPH, MS, CGC

Shadowing Prenatal Genetic Counselor, 40 hrs…….Oct. 2014-Jan. 2015
Perinatal Diagnostic Center, Thousand Oaks, CA
Genetic Counselor: Anne Dougherty, MS, CGC

RESEARCH EXPERIENCE

Intramural Researcher……...Sept. 2016-Jan. 2019
National Human Genome Research Institute, NIH, Bethesda, MD
Advisor: Dr. Lori Erby, PhD, ScM, CGC

Amgen Scholar & Continuing Volunteer Researcher……..June 2013-Jan. 2014
Genelux Corporation & Minev Lab at UCSD Moores Cancer Center, San Diego, CA
Professor: Dr. Boris Minev, PhD

Volunteer Researcher ……....Sept. 2012-Jan. 2013
Halpain Lab at Sanford Consortium for Regenerative Medicine, San Diego, CA
Professor: Dr. Shelley Halpain, PhD

TEACHING EXPERIENCE

After-School Program Coordinator.....Nov. 2014-April 2016
Maple Elementary School, Newbury Park, CA
Supervisor: Dr. Juan Santos, Ed.D

Academic Specialist……Sept. 2014-June 2016
Maple Elementary School, Newbury Park, CA
Supervisor: Dr. Juan Santos, Ed.D

Undergraduate Tutoring Assistant……..…….….Apr.-June 2014
University of California, San Diego, Division of Biological Sciences
Professor: Dr. Jayant Ghiara, PhD

LEADERSHIP EXPERIENCE

Co-Founder & Chief Editor ……Sept. 2013-June 2015
The Equilibrium, a UCSD Warren College Undergraduate Interdisciplinary Research Journal
University of California, San Diego
Supervisor: Dr. Steven Adler, PhD

Board Member…….……..Sept. 2011-June 2014
UCSD Warren College Provost's Student Advisory Council

Support Group Facilitator……..Sept. 2017
Proteus Syndrome Family Conference, Bethesda, MD

ACADEMIC PRESENTATIONS

National Human Genome Research Institute Symposium…….……Nov. 2018
Adult Patients with Undiagnosed Conditions and their Responses to Clinically Uncertain Results from Exome Sequencing

National Institutes of Health, Clinical Conference……Oct. 2018
Informal Caregivers of Dementia Patients: Addressing the Secondary Client

National Institutes of Health, Clinical Conference……...…..Feb. 2017
Communication in the Clinic with Patients without Diagnoses

UCSD Summer Research Conference……...Aug. 2013
Cancer Immunotherapy: Nanoparticle Vaccines

PROFESSIONAL TRAINING

Research

- CITI Human Subjects Research Training
- Johns Hopkins HIPAA Training “Privacy Course for Healthcare Providers”
- Johns Hopkins “Bloodborne Pathogens”
- UCSD Department of Environment, Health & Safety Courses: "Laboratory Safety Principles/ IIPP" & "Bloodborne Pathogens"

Counseling & Teaching

- Ventura County Behavioral Health's "Adolescence in the Balance: Raising an Emotionally Healthy Child"
- Brief Risk Reduction Interview and Intervention Model (BRRIIM)
- UCSD Undergraduate Tutoring Assistant Training, Division of Biological Sciences

AWARDS, HONORS, SCHOLARSHIPS

UCSD Warren College Commencement Flag Bearer ……..June 2014
Recognition of contributions to UCSD Warren College

Amgen Scholar, host institution UCSD…….2013
The Amgen Scholars program is a prestigious undergraduate research fellowship for those interested in pursuing an advanced career in science. Scholars engage in hands-on research with leading scientists at world-renowned educational institutions, participate in a weekend-long symposium at Amgen in southern California, produce a research proposal, and present their research at a conference.

Malcom R. Stacey Memorial Scholarship Recipient……2012 & 2013

Ventura County Community Foundation William A. & Cynthia D. Fairburn Memorial Scholarship Fund Recipient.……....2011

American Legion Auxiliary California Girls State Delegate ……...2010
One female delegate is chosen from each California high school to attend *California Girls State*, a prestigious week-long government and leadership program held by the American Legion Auxiliary.